skilled in the art would recognize that agents such as cholesterol would not come under this definition.

The term "vascular damaging agent", as defined in the specification to be an agent inducing damage in neovasculature, especially tumour vasculature, is widely understood and used by those skilled in the art of novel treatments for solid tumours. T he term also has two often-used synonyms within the cancer community: vascular targeting agent and anti-vascular agent. Vascular damage is also sometimes referred to as vascular shutdown and is understood to mean a lasting reduction in the ability of the vasculature to act as a carrier of blood and nutrients. (A search using the terms vascular damage (or damaging), vascular targeting, vascular shutdown and anti-vascular could identify all the prior are tin the area and the term would not be misunderstood by one skilled in the art.) The biological test for vascular damaging agents are widely agreed and well recognized. The most common is the test of reduction in perfused (functional) vascular volume within a tumor of an animal treated *in vivo* with the agent. This test is exemplified in the present case as well as in the art and can easily be reproduced by one skilled in the art. It therefore, offers a method of recognizing a vascular damaging agent. Particular classes of compound are well known as vascular damaging agents. In particular, the tubulin-binding compounds colchicine, vinblastine, vincristine, combretastatin A4, combretasatin A4 phosphate, combretastatin A1, N-acetylcolchinol and its derivatives and the compounds knows as AC-7700 AND ac-7739 are described in the art to have this activity.

The description provides a definition of the term on page 3, last paragraph where it states "Vascular damaging agents are compounds which induce selective damage to newly formed, rather than established, vasculature." The description lists specific examples of vascular damaging agents on page 4, third paragraph.

Consequently it is submitted that the term "vascular damaging agent is perfectly clear and is proper to define the metes and bounds of what is claimed.

Similarly the term"inhibitor of the formation of nitric oxide" is a term well understood by those skilled in the art. The description states on page 1, lines 31-32 "One characteristic of tumours relatively resistant to vascular damaging agents is their ability to produce large amounts of nitric oxides." The purpose of the "inhibitor of the formation or action of nitric oxide" is to reduce the amount and/or effect of nitric oxide.

On page 4, lines 1-2, it states "A wide variety of compounds which inhibit the formation or action of nitric oxide in mammalian systems can be employed.

The description goes on to describe nitric oxide synthase inhibitors in more detail and list examples on page 5, first paragraph.

The effect of the inhibitors are almost certainly medicated through a reduction in nitric oxide formation and subsequent action. A strong scientific rationale exists for the mechanism of these effects and it would definitely be expected from results that any agent which prevents formation or action of nitric oxide would have the activity.

Again, it is submitted that the use of this term is proper and complies with 35 USC 112 second paragraph.

Turning to the term "amount sufficient to augment the effect of the vascular damaging agent", again it is submitted that this is clear to one skilled in the art as to when the claim limitation has been met and so complies with 35 USC 112. One skilled in the art would immediately understand the term "vascular damaging agent". Therefore, one skilled in the art knows what "amount sufficient to augment the effect of the vascular damaging agent" means, since the other words have their ordinary dictionary meanings. The word 'augment' means to increase, to enhance, to make greater in strength.

Finally, it is not understood why the examiner questions the term "substantially simultaneously but separately." On its face, this expression seems clear. Again these words have their ordinary dictionary meaning, it means that the two agents are given separately at, or almost at, the same time. You state that this claim is clear and that you will argue against this objection. We believe that the claim is clear to any reader and to any one skilled in the art.

Turning now to the examiner's rejection of the use of the term"a vascular damaging agent other than a cytokine releasing anti-cancer releasing agent" in claim 1, it is submitted that this should be acceptable. In re Johnson and Farnham 194 USPQ 187, the Court of Customs and Patent Appeals was confronted with a claim similar to present claim 1 in which was distinguished over the prior art by a proviso that was not explicitly set out in the original description. The court set out the problem before it as follows

> The only inquiry is whether after exclusion from the original claims of two species specifically disclosed in the ... application, the ... disclosure satisfies §112 first paragraph for the "limited genus" now claimed. (194 USPQ page 195 right hand column, first paragraph of part II of the decision).

The court pointed out that what was happening was that the inventor was simply claiming less than he had disclosed and that it was for the inventor to decide what bounds of protection he would seek (last paragraph on page 195 and first paragraph on page 196) and went on to state:

> The notion that one who fully discloses and teaches those skilled in the art how to make and use a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and thus has failed to satisfy the requirements of §112 first paragraph appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. All that happened here is that the appellants narrowed their claims to avoid having them read on a lost interference count.. (page 196 right hand column, first complete paragraph)

It is submitted that the present situation is directly analogous. All that happened here is that the applicants limited their claims to avoid them reading on the prior art. Such an amendment is proper and creates no basis for a rejection under 35 USC 112. Similar

comments apply as to whether the applicants are entitled to priority from British Application 9903404.3 for claims including this limitation.

Turning now to the 35 USC 102 rejection, the Tozer reference was published after the claimed priority date of the present application. As noted above, in view of the Johnson case discussed above, it is submitted that claim 1 does not lose its entitlement to priority simply because it excludes cytokinase releasing anti-cancer agents from its definition of vascular damaging agents. Thus the only issue on priority is whether the disclosure now set out at page 6 lines 6 - 18 and pages 7 and 8 Table 3 is necessary to support a claim as now set out. It is submitted that even without this disclosure, the description is sufficient for the purposes of 35 USC 112. The data set out in the examples is not necessary to know how to put the invention into practice and merely confirms statements made elsewhere in the disclosure. Similarly knowledge of how to determine suitable dosages and formulate them which is illuminated on page 6 is in any case withing the competence of those skilled in the art. It is therefore submitted that Tozer is not a valid reference under 25 USC 102 against the present application.

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So far as the 35 USC 103 rejection is concerned, as noted above, Tozer is not a proper reference against the present claims.

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The other documents cited by the Examiner do not provide valid obviousness arguments for the following reasons.

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Narayan et al. (J. Biol. Chem. 1995, 270, 11103-10 abstract only) teaches S-alkyl-L-thiocitrullines and suggests that they may have therapeutic utility in treating hypotension due to the overproduction of nitric oxide. It does not teach the use of S-alkyl-L-thicitrullines in combination and certainly not their use in combination with vascular damaging agents. It says nothing about angiogenesis or neovasculature. The present invention relates to a novel method of treatment which is not obvious in the light of Narayan et al. Tozer et al is not prior art so the two references cannot be combined. Stenger et al. (Eur. J. Pharmacol. 1995, 294, 703-12 abstract only) teaches that L-N6-(1-iminoethyl)-lysine is a novel inhibitor of nitric oxide synthase. It does not teach the use of L-N6-(1-iminoethyl)lysine in combination and certainly not their use in combination with vascular damaging agents. It says nothing about angiogenesis or neovasculature. The present invention relates to a novel method of treatment which is not obvious in the light of Stenger et al. Tozer et al, is not prior art so the two references cannot be combined.

WO95/09621 exemplifies the combination of DMXAA and L-N-iminoethyl-ornithine (a nitric oxide synthase inhibitor) which we have excluded by the disclaimer "a vascular damaging agent other than a cytokine releasing anti-cancer agent".

D3, D4, and D5 all focus on novel inhibitors of nitric oxide. D2, D3, D4, D5 and D6 (WO95/01974) suggest the use of nitric oxide inhibitors for ameliorating the systemic hypotension which occurs in some infectious disease states and inflammatory disease conditions including the hypotension arising due to the administration of cytokine releasing agents. D8 (Chaplin D.J. et al., Seminars in Radiation Oncology, Vol. 8, no. 3, 1998, 151-

163) is a general discussion of how different agents can modify the blood flow in tumours. Nitric oxide inhibitors and vascular damaging agents are discussed separately amongst several other agents and therapies. No combinations are suggested.

D7 (WO97/32585) is directed to dithiocarbamate-containing nitric oxide scavengers and their use to reduce levels of nitric oxide.

In view of the foregoing it is believed that this application is now in order for allowance. An early action to this end is respectfully solicited. If the Examiner believes it would be useful to discuss this matter either personally or in a telephone interview, he is requested to let us know so that this can be arranged.

Respectfully submitted,

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